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# Accuracy of preoperative contrast-enhanced ultrasound in grading bladder cancer: Systematic review

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## ABSTRACT

The second most common type of cancer that urologists treat is bladder cancer, therefore, the best treatment strategies for each patient depend on early detection, accurate staging, and diagnosis. Also, its detection methods should be developed and studied frequently to be improved. This study aimed to assess the utility of contrast-enhanced ultrasound in Bladder cancer diagnosis, particularly in differentiating low-grade from high-grade bladder cancer. The Cochrane Library, EMBASE, and PubMed were used to search the literature until 2022. The criteria for inclusion were studies with patients suspected or unknown bladder cancer undergo contrast-enhanced ultrasound for preoperative diagnosis and local staging based on cystoscopy or transurethral resection. After removal of duplication, abstract and title screening, the review included five studies. Information regarding author name, year of publication, objective, study participant's characteristics, findings and conclusion were all extracted from the studies. With a mean age ranging from 60 to 68 years, the included publications featured a total of 436 bladder cancer patients. Upon contrast-enhanced ultrasound, 222 bladder cancer lesions were found to be positive, whereas 214 lesions were found to be negative; histology revealed 78 cases of muscle invasive, 118 cases of non-muscle invasive bladder cancers, 144 cases of high-grade bladder cancer, and 96 cases of low-grade bladder cancer. According to the results of our systematic review, contrast-enhanced ultrasound has a good level of diagnostic accuracy, sensitivity, and specificity.

**Keywords:** Bladder cancer, ultrasound, diagnosis

## 1. INTRODUCTION

Bladder cancer (BC), appear to be the 6th most prevalent cancer identified in men, ranks 10th in the world in terms of both new cases and cancer-related fatalities (Sung et al., 2021). More than two thirds of BC are non-muscle-invasive bladder malignancies, and the majority of BC are urothelial carcinomas (Carando et al., 2020). Tumour invasion into the muscularis

propria is referred to as muscle-invasive bladder cancer, whereas tumours restricted to the mucosa or penetration up to the lamina propria are known as carcinoma in situ (Kamat et al., 2016). Patients with tumours classified as high-grade or low-grade BC had significantly different prognoses based on histopathological staging (Montironi and Lopez, 2005). The primary course of treatment for low-grade BC, or non-muscle invasive, involves removing the entire tumour and using an intravesical adjuvant afterward. For muscle invasive or high-grade BC, radical cystectomy is currently the accepted treatment protocol, which is followed by neoadjuvant chemotherapy (Ge et al., 2018).

Therefore, for each patient, early discovery, precise staging and grading diagnosis are essential for optimising treatment plans. Transurethral resection of bladder tumour and cystoscopy are the two methods used for the definitive diagnosis of bladder cancer (Hirosu et al., 2019). However, cystoscopy is a very invasive, costly, and anaesthetic treatment that can result in hematuria and urinary tract infections. Although it has various drawbacks, transurethral resection is nevertheless a trustworthy technique in BC for determining grades and stages since it eliminates all visible pathology (Yu et al., 2006). Pathologists find it challenging to determine if a tumour has invaded the lamina propria or the muscularis propria in fragmented, disoriented, and severely cauterised specimens (Paner et al., 2010). This identification is closely related to the available treatment options.

The assessment of tissue vascularization and neoplasm perfusion is done using contrast-enhanced US (CEUS) (Serafin et al., 2016). The approach uses the perfusion of contrast agent microbubbles in the bulk to successfully discriminate between necrosis and clotting. One benefit of CEUS is that it is non-nephrotoxic, which is particularly beneficial for individuals with low GFR. In addition to monitoring BC perfusion in real time, CEUS offers a unique imaging capability that allows it to distinguish between the different layers of the bladder wall: The mucosal layer, especially in the submucosa layer, exhibits rapid and sustained high enhancement, while the bladder muscle layer exhibits slow and low enhancement (Scattoni et al., 1996). The purpose of this research was to evaluate the use of CEUS in the diagnosis of BC, specifically in identifying low-grade from high-grade BC.

## 2. METHOD

### Search strategy

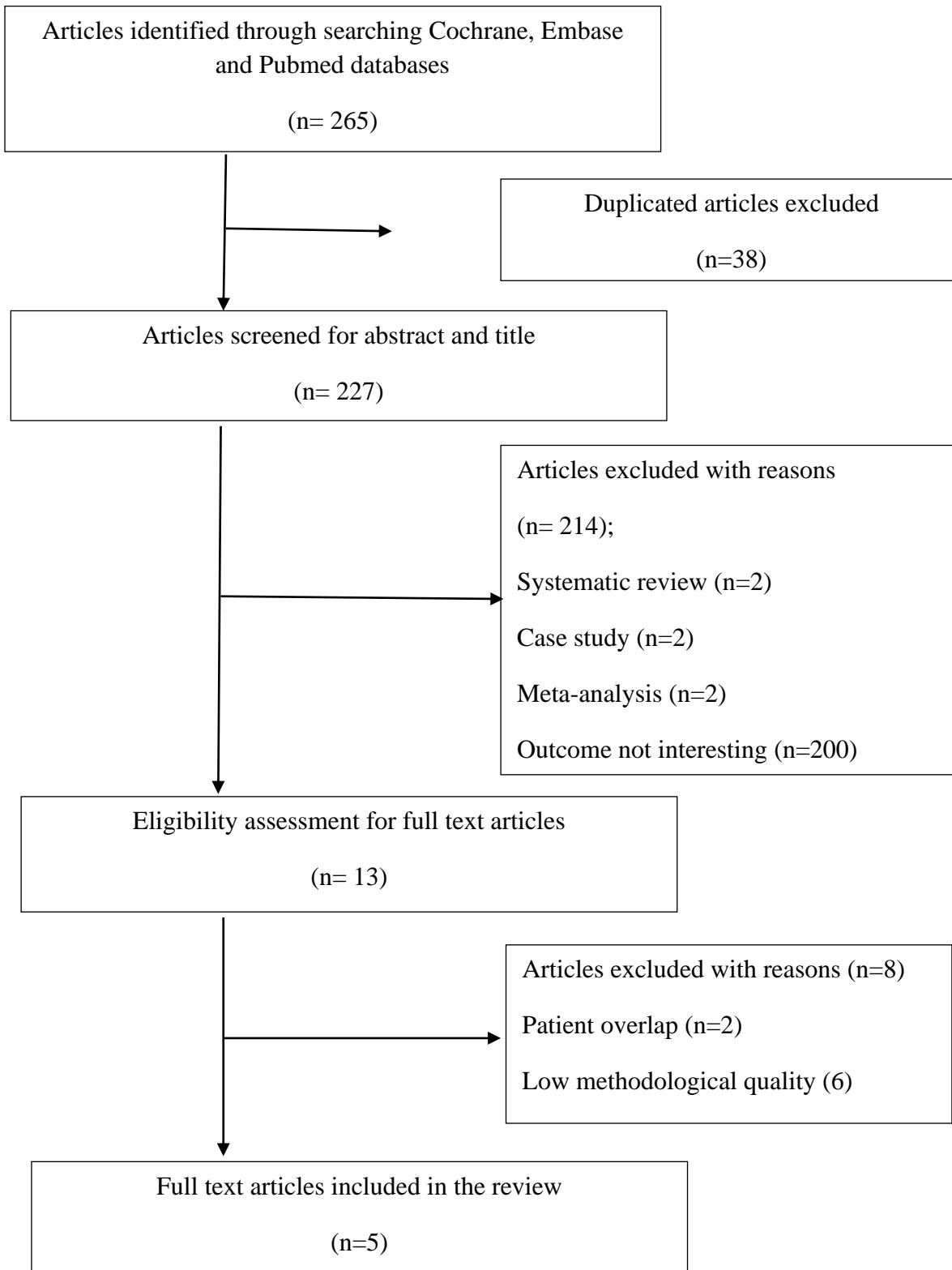
The Cochrane Library, EMBASE, and PubMed were used to search the literature until 2022. The following terms were used: Transitional cell carcinoma or bladder cancer, bladder carcinoma, bladder malignancy, bladder neoplasm, and contrast-enhanced ultrasonography. There were no linguistic barriers when conducting the literature search. The references were examined to make sure all necessary research were located, and only studies assessing the diagnosis accuracy of bladder cancer by CEUS were included. The reference standard employed in this study were transurethral resection and cystoscopy. The criteria for inclusion were studies with patients suspected or unknown BC undergo CEUS for preoperative diagnosis and local staging based on cystoscopy or transurethral resection, and that the published data allowed for the evaluation of CEUS's diagnostic performance in terms of distinguishing low-grade from high-grade bladder cancer. 38 entries were removed due to duplication after our database search turned up 265 papers.

Following a review of the titles and abstracts, 214 studies were deemed ineligible, and 8 investigations were excluded for not providing sufficient reporting on staging accuracy. Finally, the review included five studies. Information regarding author name, year of publication, objective, study participant's characteristics, findings and conclusion were all extracted from the studies. Authors organized and analyzed the data using Google Sheets and SPSS Version 24. Data from the included research were discussed by all contributors. The mean and standard deviation of the overall sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were used to estimate the results. A narrative synthesis was used to describe the type and scope of published findings within the identified research.

## 3. RESULTS

After 265 papers were found in our database search, 38 items were eliminated because of duplication. After examining the abstracts and titles, 214 papers were disqualified, and 8 investigations were disqualified for lacking reporting on staging accuracy. Ultimately, the review contained five studies (Caruso et al., 2010; Drudi et al., 2012; Li et al., 2012; Gupta et al., 2016; Li et al., 2017). The selecting procedure is explained in full in (Figure 1). With a mean age ranging from 60 to 68 years, the included publications featured a total of 436 bladder cancer patients, written by authors from China Li et al., (2017), Li et al., (2012), Italy Caruso et al., (2010), Drudi et al., (2012), and India (Gupta et al., 2016). Upon CEUS, 222 bladder cancer lesions were found to be positive, whereas 214 lesions were found to be negative; histology revealed 78 cases of muscle invasive, 118 cases of non-muscle invasive bladder cancers, 144 cases of high-grade bladder cancer, and 96 cases of low-grade BC (Caruso et al., 2010; Li et al., 2012; Gupta et al., 2016; Li et al., 2017).

Table 1 enumerates the primary features of the research that is featured. The methodological assessment found that all of the studies had a prospective design, that the included studies were of good quality, and all of the studies enrolled consecutive patients, additionally; the reference standard for treating bladder tumours was either transurethral resection or cystoscopy. The lowest sensitivity was 0.850 observed in Li et al., 2017 study (Table 2). Regarding diagnostic performance in the included studies the mean value of true negative rate, false positive rate, false negative rate and true positive rate was 38.2, 4.6, 3.4, and 41 respectively (Table 3).



**Figure 1** Consort chart of selected studies

**Table 1** Characteristics of the included studies

Citation	Study design	Study aim	Population characteristics	Main findings	Conclusion
Gupta et al., 2016	Prospective study	To assess CEUS as a potential tool for predicting the preoperative tumour grade and the T stage of bladder cancer.	Prior to endoscopic resection, 110 CAUB patients who presented to the Department of Urology had CEUS, and the results were compared with those of the histology.	Regarding identification of Ta, T1, and muscle invasion, CEUS exhibited sensitivity values of 75%, 65%, and 90% and specificity values of 95%, 85%, and 92%, respectively. CEUS had a 78% sensitivity and an 85% specificity in determining the lesion's grade.	For preoperative T staging and grading of bladder cancer, CEUS is a useful substitute. In low GFR patients the other imaging modalities were contraindicated then the use of CEUS is uniquely advantageous
Caruso et al., 2010	Prospective study	This study set out to determine how well contrast-enhanced sonography performed in comparison to traditional sonography in order to distinguish between muscle-infiltrating and superficial bladder neoplasms.	34 individuals with bladder cancers that were registered consecutively had both conventional and contrast-enhanced sonography. Two separate sonologists reviewed each examination.	Nine tumours that invaded muscles and 25 superficial tumours were found during the final pathologic staging. Of the nine muscle-infiltrating tumours, five were visible on conventional sonography and all nine were visible on contrast-enhanced sonography. While gray-scale ultrasound performed poorer in terms of diagnostic performance (area under the curve = 0.613), contrast-enhanced sonography's performance was close to that of the reference standard (area under the curve = 0.996).	Our research shown that contrast-enhanced sonography is superior to conventional sonography in the identification of muscle-infiltrating vs superficial bladder neoplasms.
Drudi et al., 2012	Prospective	Confirming the value of low mechanical index CEUS in conjunction with time-intensity curves for the distinction between high- and low-grade bladder malignant lesions.	Three types of ultrasound tests were performed on 144 patients: contrast-enhanced ultrasound, colour Doppler ultrasound, and grayscale ultrasound. All patients thereafter had a transurethral excision of the bladder tumour and a cystoscopy.	High-grade carcinomas (61.1%) and low-grade carcinomas (38.9%) were the histological diagnosis. The CDUS had a sensitivity of 87.5% and a specificity of 60%. The CEUS had a sensitivity of 90.9% and a specificity of 85.7%.	Because CEUS produces distinct contrast-sonographic perfusion curves in addition to usual enhancement patterns, it is a dependable noninvasive technique for distinguishing between low- and high-grade bladder carcinomas.
Li et al., 2012	Prospective	This study set out to determine how well three-dimensional contrast-enhanced ultrasonography could distinguish between invasive and noninvasive bladder neoplasms.	Low acoustic power contrast-enhanced ultrasound, three-dimensional ultrasound, and low-acoustic-power three-dimensional contrast-enhanced ultrasound examination were administered to 60 consecutive patients with bladder	There were 16 invasive and 44 noninvasive tumours identified by final pathologic staging. All 16 muscle-invasive tumours were visible on three-dimensional contrast-enhanced ultrasonography. Compared to three-dimensional ultrasonography and contrast-enhanced ultrasonography, three-dimensional contrast-	Contrast-enhanced three-dimensional ultrasound imaging combined with contrast-enhanced spatial visualisation is clinically helpful in objectively distinguishing between non-invasive and invasive bladder neoplasms.

			tumours.	enhanced ultrasound performed better in terms of diagnosis. For three-dimensional contrast-enhanced ultrasound, the receiver operating characteristic curves were 0.976 and 0.967; for three-dimensional ultrasonography, they were 0.881 and 0.869; and for contrast-enhanced ultrasonography, they were 0.927 and 0.929.	
Li et al., 2017	Prospective	To assess the usefulness of contrast-enhanced ultrasonography (CEUS) in separating low- and high-grade urothelial cancer.	CEUS was used to evaluate 192 individuals with bladder tumours, 110 of which had high grade urothelial carcinoma and 82 of which had low grade urothelial carcinoma.	Prospective distinction for high-grade tumours at CEUS revealed the following: 86% sensitivity, 90% specificity, 88% accuracy, 92% positive predictive value, and 82% negative predictive value. Conversely, for low-grade tumours, the values are as follows: 89% for specificity, 85% for accuracy, 88% for positive predictive value, and 89% for negative predictive value.	The significant potential of CEUS in distinguishing between low- and high-grade urothelial cancers. Given that CEUS is a non-invasive, low-cost, and effective technique. It might be a trustworthy instrument for assessing people who have bladder tumours.

Abbreviation: CEUS; contrast enhanced ultrasound, CDUS; color-Doppler ultrasonography,

**Table 2** The diagnostic performance of the included studies

Citation	Specificity	Sensitivity	True negative rate	False positive rate	False negative rate	True positive rate
Gupta et al., 2016	0.981	0.982	52	1	1	53
Caruso et al., 2010	0.913	1	21	2	0	9
Drudi et al., 2012	0.857	0.909	48	8	8	80
Li et al., 2012	0.857	1	36	6	0	15
Li et al., 2017	0.857	0.850	34	6	8	48

**Table 3** Descriptive statistics of diagnostic performance of the included studies

	Mean Difference	95% Confidence Interval	
		Lower	Upper
Specificity	0.893	0.82	0.961
Sensitivity	0.9482	0.86	1.03
True negative rate	38.2	22.93	53.46
False positive rate	4.6	0.916	8.28
False negative rate	3.4	-1.838-	8.63
True positive rate	41	4.725	77.27

#### 4. DISCUSSION

According to Chamie et al., (2013), the ten-year recurrence rates in BC patients were found to be 74.3%, and 50% of patients with stage T1 BC may have high-grade disease at diagnosis, with a 30 to 50% progression rate (Pashos et al., 2002). For this reason, the prognosis of BC patients greatly depends on the selection of effective treatment and early, accurate diagnosis modalities. The ability

to create a full dataset of the examination and use images for retrospective re-evaluation is one of CEUS's advantages over cystoscopy/transurethral resection. This will compensate for operator-dependent differences and more objectively evaluate the diagnosis results of CEUS Jokisch et al., (2020) for the Ta-T1 of BC patients who are not candidates for repeating cystoscopy. Additionally, CEUS can be a useful imaging information source and a noninvasive assessment technique for postoperative follow-up.

Our study used histology as the reference standard to primarily assess the accuracy of CEUS in the diagnosis of BC invasion degree. When we compared the diagnostic accuracy of CEUS for identifying high-grade BC from low-grade BC, we discovered that CEUS performed better when it came to BC staging and grading. According to Huang et al., (2018) and Gandhi et al., (2018) studies CEUS can match magnetic resonance imaging in terms of sensitivity and specificity regarding BC staging and grading, proving that CEUS is a highly useful imaging technique for determining the tumour invasion before to surgery. Jaeschke et al., (1994), mentioned that the likelihood ratio is a good indicator to demonstrate the diagnostic use of diagnostic studies. In our study true negative rate, false positive rate, false negative rate and true positive rate was 38.2, 4.6, 3.4, and 41 respectively.

The lamina propria invasion was not properly detected by CEUS; this thin, wispy layer is particularly difficult to see in female patients and those with thin bladders, and it typically vanishes with overdistension of the bladder. In this review we regarded the Ta and T1 lesions as non-muscle invasion bladder cancer, which would raise sensitivity and lower specificity. The outcomes were consistent with other research that had been published (Caruso et al., 2010; Drudi et al., 2012; Gupta et al., 2016). The sensitivity of CEUS in the diagnosis of bladder cancer staging was greater than that of BC grading in the Gupta et al., (2016) study, where the patients were analyzed by CEUS to forecast T stage and the grade of BC. This suggests that the diagnostic value of CEUS for staging of BC might be higher.

## 5. CONCLUSION

Our systematic review concludes that, CEUS possess a high sensitivity, specificity, and diagnostic accuracy, it also has a high efficiency in differentiating between low-grade and high-grade bladder cancer, making it a promising imaging method for determining bladder cancer grading and T staging.

### Ethical approval

Not applicable

### Funding

This study has not received any external funding.

### Conflict of interest

The authors declare that there is no conflict of interests.

### Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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